

Clinical Pharmacology

Pharmacokinetic and pharmacodynamic properties of inhaled corticosteroids in relation to efficacy and safety

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There are significant differences in the pharmacokinetic properties of inhaled corticosteroids currently available for use in treatment of asthma and this can result in differences in pharmacodynamic activity. All currently used inhaled corticosteroids are rapidly cleared from the body, but show varying levels of oral bioavailability, with fluticasone propionate having the lowest. Following inhalation, there is also considerable variability in the rate of absorption from the lung, and pulmonary residence times are greatest for fluticasone propionate and triamcinolone acetonide, and shortest for budesonide and flunisolide. Cortisol suppression is frequently used as a surrogate marker of systemic corticosteroid activity. Cortisol release displays a circadian rhythm, which can be mathematically modelled and the effects of exogenous corticosteroids on cortisol suppression established. However, when interpreting the effects of inhaled corticosteroids on cumulative cortisol suppression, it is important to take into consideration the pharmacokinetic properties of each particular drug, together with the study design and the time of administration.

RESPIR. MED. (1997) 91 (SUPPLEMENT A), 22–28

Introduction

The delivery of corticosteroids via an inhaled rather than an oral route, together with the development and introduction of corticosteroids with higher therapeutic ratios, has significantly improved the treatment of asthma. This improvement is mainly the result of better pharmacokinetic properties of corticosteroids. The ideal inhaled corticosteroid should have: prolonged residence time in the lung; high intrinsic activity; low oral bioavailability and high systemic clearance (resulting in negligible systemic side effects).

Immediately following inhalation via a metered-dose inhaler, 10–20% of the dose is deposited in the lung, whilst the majority (up to 90%) impacts on the oropharyngeal region and is swallowed (Fig. 1). Following absorption from the gastrointestinal tract, the

drug passes through the liver before entry into the systemic circulation. Some corticosteroids, particularly budesonide and fluticasone propionate are metabolised (89%, 99% respectively; 1,2), during their first pass through the liver, and thus, following oral absorption enter the systemic circulation as inactive metabolites. Most drugs, however, are not efficiently inactivated during first-pass metabolism and are able to enter the systemic circulation unchanged, resulting in extra-pulmonary effects (most of which are unwanted). It is important to note that the dose delivered to the lung will also be absorbed into the systemic circulation. Absorption from the lung is rapid (3) and, since the drug is not usually metabolised locally, extra-pulmonary effects may occur, especially from very high inhaled doses (4).

At present, five corticosteroids are available for use in the treatment of asthma: triamcinolone acetonide (TAA), flunisolide, beclomethasone dipropionate (BDP), budesonide, and fluticasone propionate. These inhaled corticosteroids differ not only in their pharmacokinetic properties, but also in their glucocorticoid receptor affinity and potency (see Table 1).

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This supplement was sponsored by Glaxo Wellcome plc.

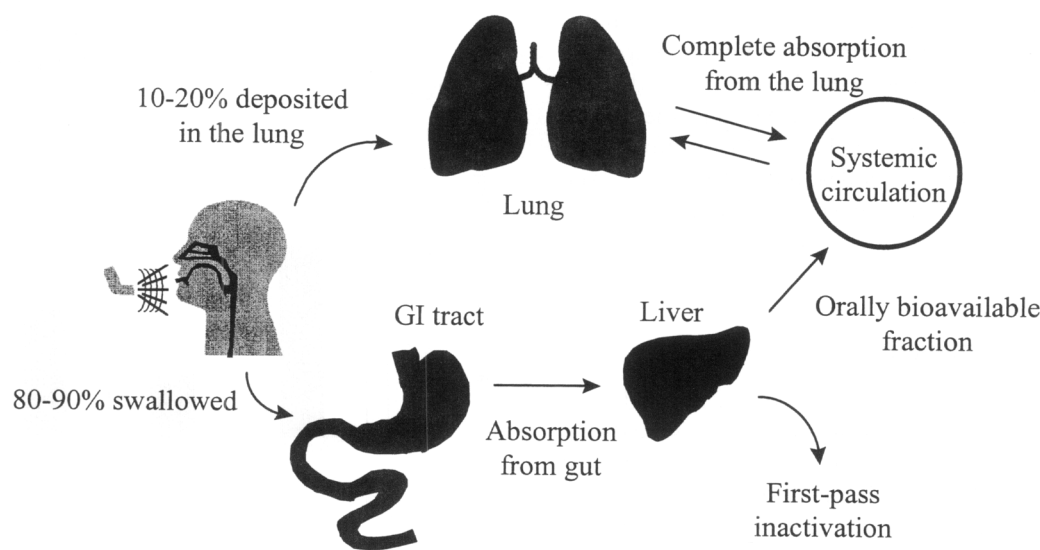


FIG. 1. Schematic representation of the pharmacokinetic fate of inhaled corticosteroids.

TABLE 1. Pharmacokinetic and pharmacodynamic parameters of inhaled corticosteroids

Drug	F _{oral} (%)	F _{inh} (%)	f _u (%)	CL (L/h)	Vd _{ss} (L)	t _{1/2} (h)	RRA
Flunisolide	20	39	20	58	96	1.6	180
Triamcinolone acetonide	23	22	29	37	103	2.0	233
Budesonide	11	28	12	84	183	2.8	935
Beclomethasone dipropionate	15	25	13	230	—	0.1	53
Beclomethasone monopropionate	—	—	—	—	—	—	1345
Fluticasone propionate	<1	16	10	69	318	7.8	1800

Abbreviations: RRA = relative receptor affinity compared with dexamethasone (RRA = 100); f_u = unbound fraction of the drug in plasma; CL = total body clearance; Vd_{ss} = apparent volume of distribution at steady-state; t_{1/2} = plasma elimination half-life; F_{oral} = oral bioavailability; F_{inh} = inhalation bioavailability.

For most of these corticosteroids, the pharmacologically active form of the drug is inhaled. However, BDP is a prodrug which is activated by hydrolysis to the mono-ester, beclomethasone-17-monopropionate (17-BMP).

Bioavailability

Inhaled corticosteroids are intended to provide their therapeutic effect at the site of delivery in the lung. In general, corticosteroids are absorbed well from the lung. However, as discussed previously, the greater part of an inhaled dose is swallowed and is therefore available for gastrointestinal absorption. Thus, the blood corticosteroid concentration represents the sum of pulmonary and orally absorbed fractions, and therefore separate assessment of the pulmonary bioavailability of those inhaled corticosteroids, that also

undergo significant oral absorption, is difficult. Of the inhaled corticosteroids currently used in clinical practice, the oral bioavailability of fluticasone propionate is the lowest with a value of less than 1% (5) compared with 23% for TAA (6), 20% for flunisolide (7), and 11% for budesonide (2). No reliable data are available for BDP. For fluticasone propionate, pulmonary bioavailability which can be calculated with greater assurance is 16–30%, depending on the inhalation device used (8). Reported pulmonary bioavailabilities of other inhaled corticosteroids are: 22% for TAA (6), 39% for flunisolide (7), and 28% for budesonide (9). Data are unavailable for BDP.

Plasma protein binding

As only the free, unbound drug is able to interact with the glucocorticoid receptor, when measuring

plasma or serum concentrations of any of the inhaled corticosteroids, it is important to know the concentration of unbound drug. For the five inhaled corticosteroids currently available, TAA has the lowest plasma protein binding (71%) (10), followed by flunisolide (80%) (11), budesonide (88%) (2), and fluticasone propionate (90%) (12). BDP has been reported to be 87% bound to plasma proteins (13), but no data are available for 17-BMP.

Volume of distribution

The volume of distribution (V_d) of an inhaled drug allows quantification of extra-pulmonary tissue distribution. The larger the V_d , the greater the amount of drug located in the peripheral tissues, but this does not necessarily indicate a higher systemic pharmacological activity, as this depends on how much drug is distributed in bound/free form. The volume of distribution at steady state ($V_{d_{ss}}$) for fluticasone propionate is 318 L (14), which is in agreement with the high lipophilicity of the drug. The $V_{d_{ss}}$ values for the other corticosteroids are reported to be 183 L for budesonide (15), 103 L for TAA (6), and 96 L for flunisolide (11). Again, no reliable data are available for BDP or 17-BMP.

Systemic clearance

Rapid clearance following absorption should minimise the systemic side-effects of an inhaled drug. In theory, the faster the systemic clearance, the higher the therapeutic index. All of the currently used inhaled corticosteroids have rapid systemic clearances of similar magnitude: 37 L/h for TAA (6), 58 L/h for flunisolide (7), 84 L/h for budesonide (2), and 69 L/h for fluticasone propionate (14). These values are approximately the same as the rate of hepatic blood flow, which is the maximum clearance rate possible for hepatically metabolised drugs. BDP was reported to have a systemic clearance greater than hepatic blood flow (230 L/h), which is indicative of extra-hepatic metabolism (16). This value is expected for BDP as extra-hepatic metabolism results in the formation of the pharmacologically active metabolite, 17-BMP. The clearance rate of 17-BMP has not been reported.

Elimination half-life

The elimination half-life of any drug is dependent on both the volume of distribution and the rate of systemic clearance. The elimination half-life quantifies how rapidly the plasma concentration changes, but does not indicate the magnitude of concentration.

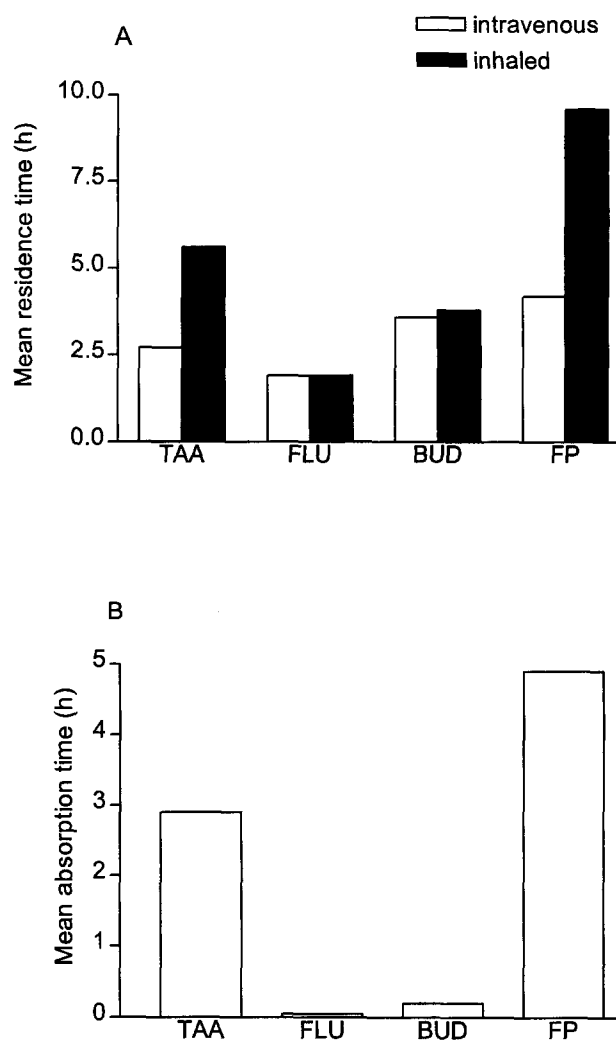


FIG. 2. Mean residence time (A) and mean absorption time (B) for triamcinolone acetonide (TAA), flunisolide (FLU), budesonide (BUD) and fluticasone propionate (FP).

For the currently used inhaled corticosteroids, fluticasone propionate has the longest elimination half-life of 7–8 h (measured following intravenous administration), which is a result of its large volume of distribution (14). The elimination half-life of TAA is 2.0 h (6), flunisolide is 1.6 h (8,17), and budesonide is 2.8 h (2). The elimination half-life of BDP was recently reported to be only 0.1 h (18), but no data are available for 17-BMP.

It is possible for the terminal half-life after inhalation to differ from the elimination half-life after intravenous administration, if absorption from the lung is slow and is the overall rate limiting step. This may be the case for fluticasone propionate, since terminal half-life values of 10 h have been reported after inhalation. Since fluticasone propionate is absorbed only via the lung, this indicates a relatively

long residence time at the pulmonary site of action (Fig. 2). Similar results have been observed with TAA, where the terminal half-life after inhalation was also found to be longer (5.6 h) than after intravenous administration (2.7 h) (6). Terminal half-lives of budesonide and fluticasone remain short after inhalation, indicating rapid absorption both from the lung and from the gastrointestinal tract (2,19). The terminal half-life of 17-BMP is reported to be 6.5 h (18), but no reliable intravenous data are available to determine whether this value is limited by absorption. However, the limitation of this method of calculating terminal half-life is that it depends on the sensitivity of measurement of blood drug concentrations. Thus, low levels of drug in the lung may remain undetected, resulting in apparently low residence and absorption times. As with V_d , residence time in the lung is not necessarily directly related to pharmacological activity, as the latter depends on whether or not the drug is in the unbound, free form. However, a long residence time in the lung indicates a long-lasting availability for topical release and action.

Accumulation

Accumulation is the increase in plasma drug concentration that occurs during multiple-dose administration until steady-state is reached. The accumulation time is a function of the terminal elimination half-life of the drug, whereas the extent of accumulation, i.e. the magnitude of the steady-state plasma drug level, is independent of the half-life and is only a function of systemic clearance. Hence, it will take longer to reach steady-state for fluticasone propionate than for budesonide, for example. However, for equal amounts of drug absorbed, the resulting steady-state concentrations will be quite similar (Fig. 3).

Relative receptor affinity

The receptor affinity of inhaled corticosteroids can be expressed relative to that of the standard, dexamethasone (relative receptor affinity (RRA) = 100). Of the currently used corticosteroids, fluticasone propionate has the highest receptor affinity (RRA = 1800), followed by 17-BMP (RRA = 1345), budesonide (RRA = 935), TAA (RRA = 233) and flunisolide (RRA = 180) (Table 1; 20). These differences in affinity for the glucocorticoid receptor means that inhaled corticosteroids should never be compared based on microgram doses, but only in terms of equipotent doses.

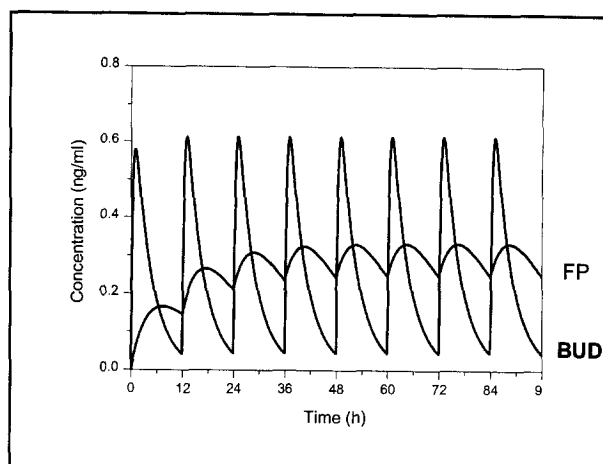


FIG. 3. Simulated plasma concentrations of fluticasone propionate (FP) and budesonide (BUD) after inhalation of a 1 mg-dose twice daily (inhaled bioavailability 25%).

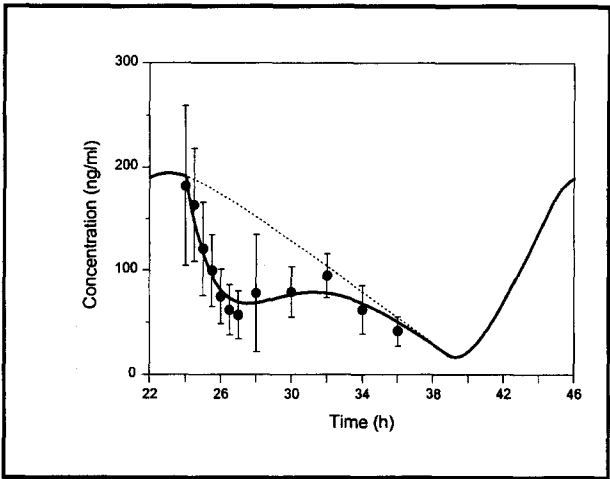
Pharmacokinetic-pharmacodynamic profiles

Cortisol suppression is the most frequently used surrogate marker of systemic activity of corticosteroids. However, cortisol release follows a circadian rhythm, which makes analysis of corticosteroid-induced cortisol suppression very complex. It is possible to use deconvolution methods to convert cortisol concentrations into cortisol release rates, which can then be described by a set of two straight-line equations (21). This model is able to describe cortisol baseline data, and furthermore, can account for cortisol suppression by exogenous corticosteroids using the equation below:

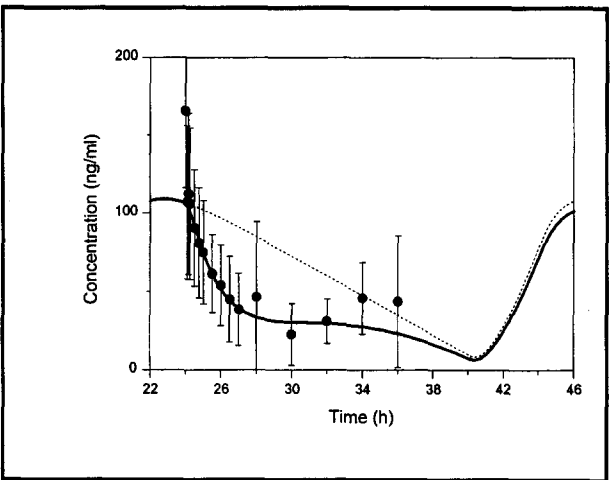
$$\frac{dC_{Cort}}{dt} = R_C \cdot \left(1 - \frac{E_{max} \cdot C_f}{E_{50} + C_f} \right) - k_e \cdot C_{Cort}$$

where C_{cort} is the cortisol concentration, R_C is the cortisol release rate [concentration/time], E_{max} is the maximum possible effect (usually 1), E_{50} is the unbound concentration of the exogenous corticosteroid that produces 50% of the maximum effect, k_e is the elimination rate constant of cortisol, and t is time (21). The measured and curve-fitted cortisol concentrations after pulmonary administration of flunisolide (19), TAA (10) and fluticasone propionate (8) are shown in Figure 4. The cumulative extent of suppression, for example over 24 hours, can be expressed as the area between the baseline and the suppressed cortisol levels. This pharmacokinetic-pharmacodynamic model allows good prediction of measured cumulative cortisol suppression as reported in several published studies (Fig. 5) (22).

A



B



C

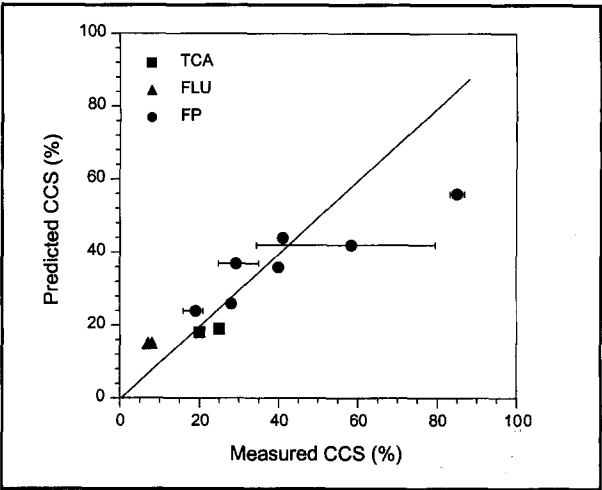
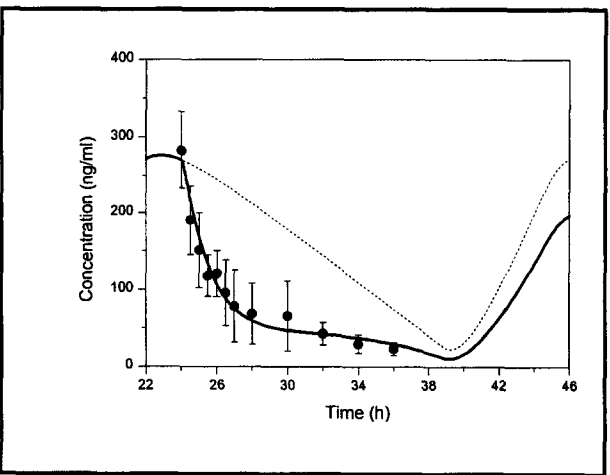


FIG. 5. Correlation between predicted cumulative cortisol suppression (CCS) as a percent of baseline and measured CCS for triamcinolone acetonide (TAA), flunisolide (FLU) and fluticasone propionate (FP) in several clinical studies. Values are expressed as mean \pm SD (where available).

When examining the suppressive effects of inhaled corticosteroids on cortisol release, it is also important to consider the time of drug administration in view of the circadian rhythm of cortisol release. A comparison of the calculated cumulative cortisol suppression after administration of inhaled flunisolide 1000 μ g and fluticasone propionate 500 μ g at either 0800 or 2000 h (23) is shown in Figure 6. As can be seen for flunisolide, a drug with a comparatively short elimination half-life, administration at 2000 h produces less cortisol suppression than at 0800 h, whereas for fluticasone propionate, which has a longer elimination half-life, there is no significant difference in cortisol suppression between morning and evening administration. It is extremely important, therefore, to critically examine the study design and drug administration time when evaluating and comparing results between such studies.

Discussion

Examination of the pharmacokinetic and pharmacodynamic properties of currently available inhaled corticosteroids reveals significant differences. While most show rapid systemic clearance after absorption,

FIG. 4. Plasma cortisol concentrations (mean \pm SD) after inhalation of 1 mg flunisolide (A), 2 mg triamcinolone acetonide (B) and 1 mg fluticasone propionate (C). Also shown is the respective cortisol baseline profile (dotted line).

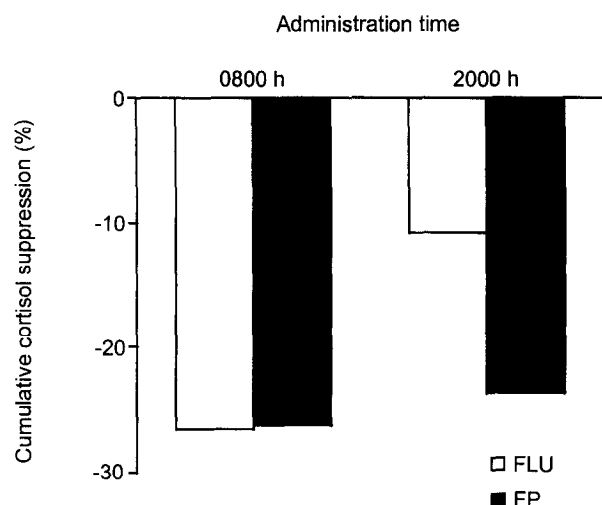


FIG. 6. Cumulative cortisol suppression over 24 hours following administration of either inhaled flunisolide 1000 µg or fluticasone propionate 500 µg at 0800 or 2000 h.

there are differences in oral bioavailability and absorption rate from the lung following inhalation. The lung absorption rate is an important property, as it reflects the pulmonary residence time, and therefore, duration of availability of the drug in the lung. Long residence times have been calculated for fluticasone propionate and TAA, whereas budesonide and flunisolide are absorbed very rapidly from the lung. Mathematical analysis of the suppressive effects of inhaled corticosteroids on cortisol levels has revealed that the pharmacokinetic properties of the drugs are responsible for some of the effects observed. Further understanding of the underlying mechanisms of asthma may improve the therapeutic index of corticosteroids in the future.

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